Appendix A

Declaration of Hans Klingemann, M.D., Ph.D., Pursuant to 37 C.F.R. § 1.132

Appendix A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Hans Klingemann	
Serial No. 10/008,955	**NATURAL KILLER CELL LINES AND METHODS OF USE**
Filed: December 7, 2001	
Art Unit: 1644	
Patent Examiner: Ronald B. Schwadron	
Attorney Docket No. 06-129PCT/US/CIP	
Confirmation No.: 5420	

DECLARATION OF HANS KLINGEMANN, M.D., Ph.D.
PURSUANT TO 37 C.F.R. § 1.132

I, Hans Klingemann, M.D., Ph.D., of Boston, Massachusetts, hereby declare that:

1. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

2. I am the sole inventor of the modified NK-92 cells disclosed in U.S. Patent Application Serial No. 10/008,955 (hereinafter, "the '955 Application"), identified above.

3. I submit this Declaration in support of the Response To Final Office Action filed on October 15, 2008.

4. I earned my Vor-Diplom in Biology from the University of Heidelberg, Heidelberg, Germany, in 1971, and my M.D. from the University of Wurzburg Medical School, Germany, in 1976. I carried out my internship in Internal Medicine and Surgery at the University of Wurzburg Medical School, Germany, from 1977-1978 and my residency in Internal Medicine at the University of Marburg Medical School, Germany, from 1978-1984. I received additional Post-graduate training in Bone Marrow Transplant/Oncology at the Fred Hutchinson Cancer Research Center, Seattle, WA, from 1984-1986.

5. I have held academic appointments at the University of Marburg Medical School (Privat-Dozent of Medicine, 1983-1986; Professor of Medicine, 1986-1987), University of British Columbia, Vancouver, CDN (Clinical Associate Professor, 1987-1995; Clinical Professor, 1995-1997), RUSH Medical College, Chicago, IL (Coleman Foundation Professor of Medicine, 1997-2004), and TUFTS University School of Medicine, Boston, MA (Professor of Medicine, 2004-present).

6. I have also held hospital/research appointments at the following facilities: Fred Hutchinson Cancer Research Center, Seattle, WA (Research Associate, 1984-1986); University of Marburg Medical School, Germany (Attending Physician, Dept. of Medicine, 1986-1987); Vancouver Hospital and Health Sciences Center, Vancouver CDN (Active Staff, Div. Of Hematology, 1987-1997); British Columbia Cancer Agency, Vancouver CDN (Active Staff, Clinical Hematology, 1987-1997); Vancouver Hospital

and BC Cancer Center, CDN (Attending Physician, Div. Of Hematology, 1987-1997); Leukemia/Bone Marrow Transplant Program of BC (Member, 1987-1997); Terry Fox Laboratory for Hematology/Oncology, BC Cancer Research Center, Vancouver, CDN (Chief, Transplantation Biology Laboratory, 1990-1997); RUSH University Medical Center, Chicago, IL (Director, Section of Bone Marrow Transplant & Cell Therapy, 1997-2004; Medical Director, Sramek Center for Cell Engineering, 2001-2004); TUFTS-New England Medical Center, Boston, MA (Senior Investigator, Molecular Oncology Research Institute, 2005-present; Director, Bone Marrow and Hematopoietic Cell Transplant Program, 2004-present); and TUFTS-NEMC Cancer Center, Boston, MA (Director, Hematologic Malignancy Program, 2007-present).

7. Additionally, I have advised numerous trainees over the course of my academic and professional careers and have taught numerous classes, both at the undergraduate and graduate levels.

8. Over the course of my career, my research projects have included studying various basic and clinical issues in transplantation immunology covering areas such as dendritic vaccines, natural killer cell biology and mesenchymal stem cells. This translational research has resulted in over 150 publications and a variety of innovative clinical trials.

9. I have authored numerous peer-reviewed publications, review papers/editorials, non-peer reviewed publications/conference proceedings, books and book chapters, and abstracts in the fields of translational research, transplantation biology, and tumor

immunology, including a number of publications relating to natural killer cells and NK-92 cells. A list of my publications is attached hereto as Exhibit 1.

10. I have also been invited to make numerous oral presentations to a variety of audiences on topics related to the fields of translational research, transplantation biology, and tumor immunology. A list of my oral presentations is included in Exhibit 1 hereto.

11. I am also a member of the following professional associations:

International Society of Experimental Hematology
American Society of Hematology
International Society for Cell Therapy
American Society for Blood and Bone Marrow Transplantation
American Society for Clinical Oncology.

12. Over the course of my academic and professional careers, I have received numerous awards and honors for my research contributions, including:

Dr. *Med.* (Magna Cum Laude)
Wolf Boas Research Award by the German Society of Gastroenterology for the best Doctoral Thesis
Habilitation (prerequisite for full professorship), University of Wurzburg Medical School, German (Ph.D. equivalent)
German Cancer Research Foundation Fellowship

13. My education, training, laboratory research, teaching experiences, and professional activities have enabled me to develop an expertise in various specialties within the field of translational research, transplantation biology, and tumor immunology, including an expertise on natural killer cells and NK-92 cells, and their use in the treatment of cancers and viruses.

14. Based on my educational background and work experience, I consider myself to be one skilled in the arts of translational research, transplantation biology, and tumor immunology, and particularly in the area of natural killer cells and NK-92 cells.

15. I am the inventor of the modified NK-92 cell line disclosed and claimed in the '955 Application.

16. I have read and am familiar with the '955 Application as it was filed in the U.S. Patent and Trademark Office and the claims of that application as currently pending in the Response To Final Office Action filed herewith.

17. I have reviewed the following prior art references cited by the Examiner of the '955 Application in the Final Office Action mailed on April 15, 2008, and am familiar with the material disclosed therein:

(a) Gong et al., Leukemia, 1994 (hereinafter, "Gong et al."); and

(b) U.S. Patent No. 5,272,082 to Santoli et al. (hereinafter, "Santoli et al.").

18. I am one of the authors of Gong et al. and am the sole inventor of the immortal cell line, NK-92, disclosed therein.

19. I have reviewed the Final Office Action issued for the '955 Application, which was mailed on April 15, 2008 (hereinafter, "Office Action"), and which contains the following statements:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Gong et al. teach use of NK-92 cells, while Santoli et al. teach in vivo use of cytotoxic cell lines. One of ordinary skill in the art would have been motivated to do so because Santoli et al. teach that lytic human derived cell lines can be used in vivo to treat disease or in preclinical in vivo studies (see column 10).

Office Action, ¶ 10.

20. The Examiner's statements are incorrect in view of the state of the tumor immunology art at the time that I invented the method of treating a pathology *in vivo* in a mammal by administering NK-92 cells, disclosed and claimed in the '955 Application. One skilled in the art would *not* have combined either Gong et al. with Santoli et al. at that time for at least the reasons set forth in paragraphs 21-40, *infra*.

21. Gong et al. disclosed the NK-92 cell line that I established from peripheral blood mononuclear cells of a fifty-year-old male patient who was diagnosed with an aggressive LGL lymphoma in 1992.

22. At the time that Gong et al. was written, I thought that the NK-92 cell line provided a suitable model to study the biology of NK-cells and activated NK-cells.

23. All experiments disclosed in Gong et al. were performed *in vitro*. Gong et al. partially characterized the cytotoxic profile of NK-92 cells.

24. The Examiner's characterization of Gong et al. is incorrect for at least the following reasons:

a. The Examiner incorrectly states that "Gong et al. teach use of NK-92 cells to lyse leukemic tumor cells." *See* Office Action, ¶ 10. Rather, Gong et al. teach that NK-92 cells demonstrated cytotoxicity against two human leukemic cell lines, but do not teach that NK-92 cells are capable of lysing various tumor cells, including other leukemic tumor cells, of different origin or type.

c. While Gong et al. do not specifically teach that NK-92 cells are unacceptable for *in vivo* use, there is no teaching, suggestion, or motivation in Gong et al. that would lead one skilled in the art to use the NK-92 cell line *in vivo* to lyse tumor cells or as a cancer treatment, much less successfully reduce such a use to practice as a method of treating mammals. In fact, I did not initially recognize the importance or utility of the NK-92 cell line in a clinical setting.

25. Santoli et al. disclose genetically modified cytotoxic T lymphoblastic leukemia cell lines (T-ALL) 104, 107 and 103/2 and their use to treat cancer, both *in vivo* and *ex vivo*. The disclosure in Santoli et al. is limited to T-ALL cells. There is absolutely no teaching or suggestion in Santoli et al. with respect to cell lines in general, or with respect to NK-92 cells in particular, nor is their use described.

26. In fact, I was not aware of Santoli et al.'s T-ALL cell lines at the time that I created the unmodified NK-92 cell line (available from American Type Tissue Collection (ATCC) as Deposit No. CRL-2407) disclosed in Gong et al. or at the time that I arrived at the method of treating a pathology *in vivo* in a mammal by administering NK-92 cells disclosed in the '955 Application.

27. As one skilled in the art, it has been my experience that know-how with respect to one cell line cannot automatically be transferred or applied to another cell line, even where the cells are closely related, including with respect to culture conditions, requirements for growth factors such as IL-2, survival and signaling patterns following adoptive transfer, ability to migrate to tumor sites, sensitivity to chemotherapeutic agents, response to staining with vital dyes, ability to maintain their cytotoxic activity following

radiation, and susceptibility to gene transfer. Furthermore, the know-how required to use a specific cell line as a method of treatment cannot automatically be transferred or applied to another cell line and is dependent on the distinguishing characteristics of each cell line. Simply because one cell line has a specific utility does not mean that other closely related cell lines will have the same utility. Each must be proven independently and the specific conditions necessary for successful results, including treatment, determined.

28. In fact, as set forth below, the T-ALL cell line is not even comparable or related to the NK-92 cell line that I developed and disclosed in Gong et al. Accordingly, there was no reason apparent to one skilled in the art at the time I arrived at the claimed method of treating a pathology *in vivo* in a mammal by administering NK-92 cells to look to Santoli et al.'s teaching of of T-ALL cells for any teaching with respect to methods of treatment with NK-92 cells.

a. The T-ALL cell lines were derived from a patient with ALL, whereas the NK-92 cell line was derived from a patient with an aggressive LGL lymphoma. These two diseases, leukemia and lymphoma, are in different disease categories and the cells derived therefrom are different cell lineages. As such, the cell lines each have unique characteristics in culture and in undergoing proliferation. One skilled in the art would therefore assume that these two cell lines are different and that conclusions with respect to one of the cell lines cannot be drawn to the other cell line.

b. T-ALL cells are of T-cell origin, are CD3-positive (a specific T-cell marker), CD8-positive, rearrange and express the T-cell receptor, are TCRαβ-positive, and are characterized by specific choromosomal translocations. *See* Santoli et al., 1:68, 2:14, and 4:27. In addition, T-ALL cells lack natural cytotoxicity receptors such as NK-44 receptors that are found on NK-92 cells. In contrast, the NK-92 cell line is a true NK cell line (i.e., it is derived specifically from natural killer cells). NK-92 cells are CD3-negative, CD8-negative, do not express or rearrange the T-cell receptor complex (TCR), and have different chromosomal rearrangements than T-ALL cells. As such, one cannot infer the behaviors, transfectability, or cytotoxic mechanisms of NK-92 cells from those of T-ALL cells because the cells have different phenotypes.

c. NK-92 cells have unusual requirements for sub-culturing. Specifically, when cultured *in vitro* in α-minimum essential medium (α-MEM), the American Type Culture Collection (ATCC; Manassas, VA) recommends the media be supplemented with, among other things, 0.2 mM inositol, 0.1 mM 2-mercaptoethanol, 0.02 mM folic acid, 100-200 U/ml recombinant IL-2 (otherwise the cells die after 72 hours), and most surprisingly, a large proportion (25%) of two sera: 12.5% horse serum and 12.5% fetal bovine serum (FBS). In earlier passages, hydrocortisone is necessary. The cell density in culture is critical, and must be regularly checked and regulated by medium changes. The medium formulation, IL-2 concentration, serum concentration and cell density must be carefully regulated throughout the culture period. The culture of these cells is in

contrast to T-ALL cells, which require fetal bovine serum for growth and proliferation, and is similar to other well-established cell lines (or even hybridomas), such as Madin-Darby Canine Kidney (MDCK) cells, which can thrive in simple MEM with 5% (FBS) and 2mM L-glutamine, 10mM N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), and sub-culturing once or twice a week.

d. Santoli et al. teach that T-ALL cells require antibody stimulation with CD2 or CD3 (a specific T cell marker) antigens to express (IFN)-γ, TNF-α, and GM-CSF. *See* Santoli et al. 2:18, 2:47. NK-92 cells do not require antibody stimulation to express (IFN)-γ, TNF-α, and GM-CSF, but rather release these cytokines in response to stimulation by IL-2.

e. Additionally, NK-92 cells are more stable than TALL-104 cells. Tam et al. (Hum. Gene Ther., 10: 1359-1373, 1999) have shown that NK-92 (both wild-type and transfected cells) cells require > 500 Gy to suppress proliferation, while Santoli et al. reported that TALL-104 cells require 40 Gy irradiation to suppress proliferation (*see* Santoli et al., Cancer Res., 56: 3021-3029, July 1996). Additionally, NK-92 cells maintain cytotoxicity and function even after irradiation, while T-ALL cells lose some cytotoxicity when irradiated.

f. Santoli et al. also reported that the standard treatment protocol for clinical trial in dogs required that the dogs be immunosuppressed using CsA, an immunosuppressive drug, starting the day before TALL-104 injections began and continuing through the first two weeks of TALL-104 injections. *See* Santoli et al.,

Cancer Res., 56: 3021-3029, July 1996). NK-92 cells do not require supplemental immunosuppression. These data suggest that TALL-104 cells are immunogenic while NK-92 cells are not.

29. Accordingly, given these significant phenotypic and functional differences between NK-92 cells and T-ALL cells, there was no reason apparent to one skilled in the art at the time I developed the method of treating a pathology *in vivo* in a mammal by administering NK-92 cells to look to Santoli et al.'s teaching of T-ALL cells to arrive at similar method of treatments. Because of the distinctive differences between these cell lines, the applicability and necessary requirements to use one of these cell lines as a method of treating *in vivo* is not applicable to the other, or any other cell line for that matter. The usefulness and necessary requirements for each would have to be characterized independently.

30. For at least the reasons set forth in paragraphs 21-29, *supra*, it would not have been obvious to one skilled in the art at the time the method of treating a pathology *in vivo* in a mammal by administering NK-92 cells was made to have combined the teachings of Gong et al. with Santoli et al. Most certainly one skilled in the art would not have had a reasonable expectation of success. If one skilled in the art were to have applied the teachings of Santoli et al to the NK-92 cells disclosed in Gong et al, they would not have had successful results because of the unique characteristics and requirements of these cells.

31. Additional comparative studies of NK-92 cells and TALL-104 cells further demonstrate that these cell lines are functionally quite different, with NK-92 cells having

significantly higher cytotoxic activity than TALL-104 cells. For example, many hematological cancers are susceptible to killing by NK-92 cells, whereas these cancers are mostly resistant to lysis by TALL-104 cells.

32. In fact, data disclosed in the '955 Application demonstrate that NK-92 cells are more cytolytic than TALL-104 or YT cells. *See* '955 Application, Tables 5 and 6, Fig. 9.

33. Notably, the results demonstrating that the NK-92 cell line is a superior cell line to the TALL-104 cell line were surprising.

34. Given the significant phenotypic and functional differences between NK-92 cells and T-ALL cells and the cytotoxic superiority of NK-92 cells to TALL-104 cells, there was no reason apparent to one skilled in the art as of the filing date of the '955 Application to look to Santoli et al.'s teaching of TALL cells for treatment of disease for any teaching with respect to the NK-92 cells disclosed in Gong et al.

35. Neither of the references cited by the Examiner in the Final Office Action, either alone or in combination, teach or suggest the method of treatment with NK-92 cells disclosed and claimed in the '955 Application and therefore these references do not obviate the claimed method of treating a pathology *in vivo* in a mammal by administering NK-92 cells. In fact, we recently published in Cytotherapy (10(6): 625-632, 2008) Phase I trial results using NK-92 cells based on methods tailored to NK-92 cells, which are very different from methods tailored to TALL cells, and not disclosed or suggested in Santoli et al or Gong et al. *See* Exhibit 2 attached hereto. The results are promising and encourage continued development of the use of NK-92 cells as a method of treatment.

36. Signed at Boston, MA, this 15 day of Oct., 2008.

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EXHIBIT 1

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EXHIBIT 2

NK-92 phase I trial

International Society for Cellular Therapy ISCT

Cytotherapy (2008) Vol. 10, No. 6, 625–632

Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: a phase I trial

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Background

Renal cell cancer and malignant melanoma are two types of cancer that are responsive to immunotherapy. In this phase I dose-escalation study, the feasibility of large-scale expansion and safety of administering ex vivo-expanded NK-92 cells as allogeneic cellular immunotherapy in patients with refractory renal cell cancer and melanoma were determined.

Methods

Twelve patients (aged 31–74 years) were enrolled, three per cohort at cell dose levels of $1 \times 10^8/m^2$, $3 \times 10^8/m^2$, $1 \times 10^9/m^2$ and $3 \times 10^9/m^2$. One treatment course consisted of three infusions. Eleven patients had refractory metastatic renal cell cancer; one patient had refractory metastatic melanoma.

Results

The NK-92 cells were expanded in X-Vivo 10 serum-free media supplemented with 500 U/mL Proleukin recombinant human interleukin-2 (rhIL-2), amino acids and 2.5% human AB plasma. Final yields of approximately 1×10^9 cells/culture bag (218–250 × expansion) over 15–17 days were achievable with ≥ 80% viability. Infusional toxicities of NK-92 were generally mild, with only one grade 3 fever and one grade 4 hypoglycemic episode. All toxicities were transient, resolved and did not require discontinuation of treatment. One patient was alive with disease at 4 years post-NK-92 infusion. The one metastatic melanoma patient had a minor response during the study period. One other patient exhibited a mixed response.

Discussion

This study establishes the feasibility of large-scale expansion and safety of administering NK-92 cells as allogeneic cellular immunotherapy in advanced cancer patients and serves as a platform for future study of this novel natural killer (NK)-cell based therapy.

Keywords

cancer, cell therapy, NK-92, phase I.

Introduction

Treatment options remain very limited for patients with metastatic renal cancer and metastatic melanoma. Median survival is 7–10 months for metastatic renal cancer and metastatic melanoma and both diseases are resistant to chemotherapy and/or radiotherapy [1]. Both cancers, however, seem to be responsive to immunotherapy [2–4] and cellular immunotherapy is increasingly being considered as a form of treatment that is non-cross-reactive with prior chemotherapy and radiation [5,6].

Natural killer (NK) cells are particularly attractive for adoptive cellular immunotherapy because of their unique ability to lyse target cells without priming [7]. Autologous NK cells from cancer patients, however, may be dysfunctional and may not recognize the malignant target. Autologous NK cells may also be inhibited by 'self' HLA expression and some tumors may in fact express functional HLA antigens (Ag) capable of inhibiting NK cell function. Allogeneic NK cells, therefore, potentially represent a better NK cell product for immunotherapy. NK-92 is a human NK-cytotoxic cell line that represents a pure allogeneic activated NK cell source. NK-92 is interleukin-2 (IL-2) dependent, lacks killer cell inhibitory receptors (KIR) and is broadly cytotoxic against a variety of hematologic and solid tumor cell lines, including leukemia, lymphoma, malignant melanoma, prostate cancer and

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DOI: 10.1080/14653240802301872

breast cancer [8]. *Ex vivo* expansion of NK-92 under good tissue practice (GTP) conditions for clinical use has allowed its entry into phase I study as a novel immunotherapy in advanced cancers [9]. The NK-92 cell line is originally derived from a non-Hodgkin's lymphoma with large granular lymphocyte morphology and a $CD56^+CD3^-CD16^-$ immunophenotype. Studies in SCID mice have confirmed that NK-92 inoculation itself is not leukemogenic. The tumoricidal activity of NK-92 against human leukemias has been tested *in vitro* against leukemic cell lines and primary leukemia cells, as well as *in vivo* by adoptive transfer of NK-92 cells into xenografted SCID mice, with the result of prolonged survival and no signs of leukemia development [10]. NK-92 infusion has further been found to prolong survival in SCID mice inoculated with human malignant melanoma cells, an observation that served as the basis for this clinical trial [11].

The objective of this study was to determine the safety of infusing NK-92 cells in patients with advanced renal cell cancer and melanoma. The three infusions, each given 48 h apart, had no severe side-effects and several patients showed objective anti-tumor responses, suggesting further exploration of this cellular treatment modality in selected cancer indications is warranted.

Methods

Patient eligibility

The study was open from April 2002 to June 2004 at Rush University Medical Center (Chicago, IL, USA). The protocol was approved by the Institutional Review Board and had obtained FDA investigational new drug application status for the *ex vivo* expansion of NK-92 cells. All patients signed informed consent before any study-related procedures. Patients with histologically confirmed metastatic renal cell cancer or malignant melanoma refractory to, or having failed, standard therapy, including surgery, radiation and chemotherapy, were eligible for treatment on this protocol. All patients had measurable disease [by computed tomography (CT) scan or physical examination] and had undergone several prior treatments, including high-dose IL-2 therapy and allogeneic stem cell transplant (SCT). Other eligibility criteria included ECOG 0 or 1, white blood cells (WBC) $>2.0 \times 10^9$/L, Hb >8 g/dl, platelets $\geq 75 \times 10^9$/L, creatinine <2.0 mg/dL and total bilirubin <2.0 mg/dL. Exclusion criteria included ECOG ≥ 2 and concurrent treatment with corticosteroids and/or other immunosuppressive drugs.

Trial design

The trial was a single-center, open-label, dose-escalation study. Three patients were treated at each dose level: 1×10^8 cells/m^2, 3×10^8cells/m^2, 1×10^9 cells/m^2 and 3×10^9cells/m^2. One treatment course consisted of three infusions of the cell dose over 48 h. Infusion days were designated as days 1, 3 and 5. The rationale for the schedule was to infuse as many NK-92 cells before a T-cell directed immune response would theoretically occur.

Manufacturing of the NK-92 cell product

Manufacturing of clinical-grade NK-92 cells was performed under GTP conditions at the Sramek Center for Cell Engineering at Rush University Medical Center [9]. At 3 weeks before the targeted date of infusion, NK-92 cell cultures were initiated from the NK-92 Working Cell Bank. NK-92 cells were expanded in X-Vivo 10 serum-free medium supplemented with 500 U/mL Proleukin recombinant human (rh)IL-2, 0.6 mm l-asparagine, 3 mm l-glutamine, 1.8 mm l-serine and 2.5% human AB plasma. The cultures were initiated at 2.5×10^5 cells/mL in 25 mL (6.25×10^6 cells) in 1-L Vuelife culture bags (American Fluoroseal Corp., Gaithersburg, MD, USA), with the addition of media every 3 days, maintaining a density of 2.5×10^5 cells/mL, and with daily mild disruption of cell aggregates. Final yields of approximately 1×10^9 cells/culture bag (218–250-fold expansion) over 15–17 days was achievable, with $\geq 80\%$ viability. After quality control verification and quality assurance release that included Gram stain, culture and mycoplasma testing, the final NK-92 cell product was resuspended in GM-2 medium (Plasma-Lyte-A medium supplemented with 2.5% human AB plasma) and infused fresh. The last feeding with rhIL-2 and fresh medium was 48 h before the first day of infusion of the expanded NK-92 product. In addition, after completion of the cell culture period, a standard cytotoxicity assay was performed to assess the functional capacity of the *ex-vivo*-expanded NK-92 cells. Calcein AM-labeled K562 and Raji cells were used as targets to determine NK-92 cell cytotoxicity of the *ex vivo*-expanded cells. The NK-92 cells were irradiated with 1000 cGy prior to infusion into the patient (Cesium Source-Blood Bank, Rush University Medical Center).

On the day of infusion, hydration (200 mL NS/h) was given to the patient 2 h prior to the NK-92 cell infusion and continued for 2 h after NK-92 infusion. The total volume of the NK-92 cell product infusate was

100–200 mL, depending on the body weight of the individual patient. The cells were infused at a rate of 5 mL/min, with a total infusion time of approximately 20–30 min. All patients received premedication with diphenhydramine before the start of each cell infusion.

Of note, the NK-92 cell line was being commercialized during the course of the clinical trial.

Treatment and follow-up

Complete tumor staging was performed prior to NK-92 treatment. During cell infusion, patients were closely monitored, with vital signs recorded at 0, 15, 30, 60, 90, 120 and 240 min and every 24 h thereafter. Patients were examined daily for clinical toxicity from NK-92 infusion for the first 7 days and then weekly thereafter until 4 weeks after cell infusion. NCI-CTC version 3 criteria were used to document toxicities. CBC and chemistries were performed daily during the treatment course. CT scans were repeated at 2 and 4 weeks after the treatment course to assess disease response, and thereafter per routine by their local oncologist. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) [12]. Additionally, a minor response was defined as regression of target tumor lesions by 10–30% with no new lesions and no non-target lesion progression. A mixed response was defined as the regression of some lesions but simultaneous progression of others.

Cytokine assays

Patient sera were collected pre-NK-92 cell infusion (time 0), at 4 h after each infusion on days 1, 3 and 5, and at 7 days post-infusion. The sera at each time point were tested by enzyme-linked immunosorbent assay (ELISA) with a standard multiplexed panel of cytokines (Linco Diagnostic Services Inc., St Charles, MI, USA). The cytokine panel consisted of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, interferon (IFN)-γ, granulocyte–macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor (TNF)-α. Four patients had cytokines measured at the higher NK-92 dose level with the hypothesis that the higher cell dose of NK-92 would tend to be more effective.

HLA antibody production

High-resolution DNA typing of the NK-92 cell line was used to establish its HLA type. High-resolution DNA typing for HLA was also performed on two patients for whom 1–2 year follow-up blood samples were available. The patient HLA class I and class II antibody (Ab) production against NK-92 was determined for these samples using standard cytotoxic cross-match and flow cytometric cross-match testing.

Statistical analysis

Analyzes were descriptive and graphical. Under the cytokine analysis, a one-sided sign-test was applied to the data from the four patients who had cytokines measured, to test the significance of the average of pre–post differences.

Results

Patient characteristics

The characteristics of the 12 patients enrolled in the study are summarized in Table 1. The median age was 50 years (range 31–74 years); eight patients were male and four were female. Eleven patients had refractory metastatic renal cell cancer, predominantly clear cell type. One patient had refractory metastatic melanoma, spindle cell type. Prior therapies included nephrectomy, high-dose IL-2, IFN, radiation, chemotherapy and SCT.

Table 1. Baseline characteristics of patients treated with NK-92 ($n = 12$)

Variable	Summary
Median age (years)	50 (range 31–74)
Gender	
Male	8
Female	4
Type of tumor	
Renal cell carcinoma	11
Melanoma	1
Metastatic sites	
Lung	10
Liver	4
Brain/central nervous system	1
Bone	3
Lymph nodes	6
Other	2
Prior therapies	
Surgery	11
IL-2, other immunotherapy (IFN, thalidomide)	10
Chemotherapy	3
Stem cell transplant	1
Radiation	4
Vaccine	1

Toxicity

All 12 patients received the three infusions of NK-92 per protocol and there were no delays in the infusion days. Table 2 summarizes the NK-92-related toxicities during the treatment course. Three patients (patients 8, 9 and 12) experienced grade 1 fevers (range 38.2–38.7°C) during the course of NK-92 infusion and all occurred with the higher dose level of $1 \times 10^9/m^2$. The fevers were self-limited and did not require treatment. The patient with metastatic melanoma developed a temperature of 41°C 4 h after the third infusion of NK-92, which responded to hydrocortisone 100 mg intravenously (i.v.). Blood and urine cultures, as well as culture of the NK-92 bag, were negative. This patient had new onset softening of his bulky pre-auricular and occipital tumor masses with frank drainage from the pre-auricular mass as it softened. There were no serious infections reported for patients at the 1-year follow-up post-NK-92 infusion.

Toxicities that were attributed to the underlying tumor and unrelated to NK-92 infusion included grade 2 neck and chest pains and grade 3 back pain in a patient with bulky retroperitoneal renal cell cancer. One grade 4 hypoglycemic episode (glucose <20 mg/dL) with symptoms of confusion and seizure-like activity occurred immediately after the first NK-92 infusion in a non-diabetic patient (11) who had extensive liver metastases. The patient's baseline glucose was normal at 162 mg/dL. The hypoglycemia responded to D50 bolus followed by continuous D5 i.v. infusion overnight. No further hypoglycemia episodes occurred with the subsequent two NK-92 infusions.

Clinical outcomes

The follow-up on this study is now 4 years, with all patients followed until death. Patients were allowed to seek other therapies after the 4-week toxicity monitoring period. As a phase I study, the study was not designed to evaluate formally the tumor response or duration of response. One patient (6) had a transient mixed response during the monitoring period. She had extensive metastases in the bilateral lungs, hila, mediastinum, abdominal and retroperitoneal nodes. The mixed response occurred as progression in the mediastinum but reduction in lung masses. She ultimately progressed and died at day 168 post-treatment. Patient 10, with melanoma, had a minor response in a target lesion at the left upper neck that was documented at 2 weeks post-infusion by physical examination and CT scan (Figure 1a,b). This patient, with very advanced disease, subsequently progressed and received alternative therapy, but did survive to 255 days post-NK therapy. Of the 12 patients who completed NK-92 treatment, 11 have subsequently died, 10 from progressive disease. Patient 3, who underwent reduced-intensity allogeneic sibling-matched transplant subsequent to NK-92 treatment, died 2.5 years later from consequences of the post-transplant immunosuppressed state, with bronchopneumonia and no active renal cell cancer. Patient 7 is the only surviving patient post-NK-92 infusion. He had progression at 4 weeks post-NK-92 infusion and went on to receive salvage therapies as allowed by the protocol. He was alive with disease and seeking further therapy for renal

Table 2. Adverse events in patients receiving NK-92 infusions. The severity of adverse events was graded according to NCI-CTC version 3

Subject	Diagnosis	Cell dose/$m^2 \times 3$ doses	Adverse event w/grade (possibly related)
1	RCC	1×10^8	0
2	RCC	1×10^8	0
3	RCC	1×10^8	0
4	RCC	3×10^8	0
5	RCC	3×10^8	0
6	RCC	3×10^8	0
7	RCC	1×10^9	0
8	RCC	1×10^9	1, fever
9	RCC	1×10^9	1, fever
10	Melanoma	3×10^9	3, fever
11	RCC	3×10^9	4, hypoglycemia
12	RCC	3×10^9	1, fever

RCC, renal cell cancer.

Table 3. Clinical outcomes

Subject	Diagnosis	Cell dose/m^2 × 3 doses	Outcome at 4 weeks	Deaths (unrelated to NK-92)
1	RCC	1×10^8	PD*	D1006, PD
2	RCC	1×10^8	PD	D101, PD
3	RCC	1×10^8	PD†	D832, bronchopneumonia
4	RCC	3×10^8	PD	D666, PD
5	RCC	3×10^8	PD	D188, PD
6	RCC	3×10^8	Mixed	D168, PD
7	RCC	1×10^9	PD	Alive D1450
8	RCC	1×10^9	SD	D212, PD
9	RCC	1×10^9	SD†	D1059, PD
10	Melanoma	3×10^9	MR	D255, PD
11	RCC	3×10^9	SD	D695, PD
12	RCC	3×10^9	SD	D466, PD

*RCC, renal cell cancer; PD, progressive disease; SD, stable disease; MR, minor response; D, day. *prior alloSCT; †subsequent alloSCT.*

cell cancer at the latest follow-up, on day 1450 post-NK-92.

Laboratory findings

There was a trend of LDH elevations that occurred with NK-92 infusion at the higher cell dose level of $1 \times 10^9/m^2$ (Figure 2). Patient 8 went from a baseline LDH of 185 U/L to 1269 U/L (normal 200–650 U/L) after the first NK-92 infusion, peaked at 2157 U/L after the third infusion, and remained elevated through day 7 (1493 U/L). Patient 11, with the hypoglycemic episode, had a dramatic increase in her serum LDH to 1219 U/L at 4 h after the first NK-92 infusion. The LDH remained elevated through the subsequent two infusions, 1536 and 1254 U/L, respectively, but normalized at day 14 of the treatment course to 237 U/L. Patient 10, with metastatic melanoma, who developed high-grade fever and a clinical tumor response, similarly had elevation from a baseline normal LDH of 409 U/L to a peak of 791 U/L and 763 U/L on infusion days 3 and 5, respectively, with ultimate normalization to 327 U/L at day 14.

Other laboratory parameters examined did not show clinically significant changes in total WBC, platelets, neutrophil count, lymphocyte count or eosinophil count in patients over the three NK-92 infusions or in the 4 weeks of follow-up.

Cytokines were measured in four of the higher cell dose patients' sera pre-, at 4 h post- each of the three NK-92

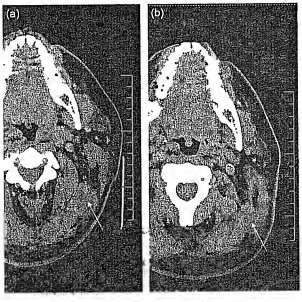

Figure 1. (a) Patient 10, pre-NK-92 infusion, left upper neck mass, 3.15 × 2.54 cm. (b) Two weeks post-NK-92 infusion, shrinkage of left upper neck mass, 2.46 × 1.76cm.

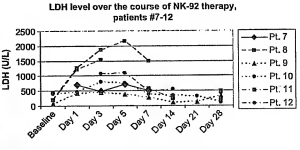

Figure 2. Trend of LDH elevation during NK-92 infusion starting at $1 \times 10^9/m^2$ cell dose. After an initial increase during treatment, the LDH values return to baseline by day 14.

infusions, and at 7 days post-infusion. Positive elevations in IL-6, IL-8 and IL-10 cytokines were seen with NK-92 infusion at the higher cell doses, perhaps suggesting tumor lysis. In patient 10, with metastatic melanoma, clinical tumor shrinkage correlated with a massive rise in IL-6, to 6819 pg/mL from a baseline of 17 pg/mL, along with grade 3 fever. IL-8 and IL-10 similarly rose (Table 4) and then normalized by day 7 post-infusion. Another observation was in patient 9, with metastatic renal cell cancer, who had baseline elevations of IL-4, IL-6 and IL-8, possibly reflecting constitutive cytokine secretion from the renal tumor.

As only four patients had cytokines measured, the sample size limited the degree of statistical reliability. However, if the IL-6, IL-8 and IL-10 pre–post differences (three per patient) are averaged within patients, in all four patients the average pre–post difference was always positive. This has a one-sided sign-test *P*-value of 0.0625, which is the smallest *P*-value obtainable in a non-parametric test with only four patients.

High-resolution HLA typing for NK-92 was confirmed as follows: A3, A11; B7, B44, $Bw4^+$, $Bw6^+$; Cw*07(3R), Cw*1601(3R); DR7, DR15; DQ2, DQ6; $DR51^+$, $DR52^-$, $DR53^+$. Samples from two patients (1 and 11) were tested for the development of anti-HLA Ab against NK-92. Patient 1 was found to have both HLA class I and class II Ab to the NK-92 cell line at 2 years post-exposure. Cytotoxicity and flow cytometric cross-match assays were also positive for this patient. For patient 11, panel reactive Ab and cross-match assays were negative at 1 year post-exposure.

Discussion

The development of the continuously growing NK-92 as a universal donor of highly cytotoxic tumoricidal cells is attractive for allogeneic cellular immunotherapy. Renal cell cancer and melanoma were chosen as the target diseases for this trial based on their previously reported immune responsiveness as tumors [2–4].

The main objective of the phase I trial was to determine the feasibility and safety of administration of NK-92 cell therapy with multiple infusions in these advanced cancer patients. NK-92 cells were successfully expanded under GTP conditions, on average 200–fold over 15–17 days with $\geq 80\%$ viability. Infusional toxicities were generally minimal, limited to grade 1 fevers. No severe hemodynamic or hematologic toxicities were seen with the NK-92 infusion, and thus it compares favorably with other cellular immunotherapies that have used autologous NK or allogeneic haplo-identical NK cells [13–18].

The two major toxicities of grade 3 fever and grade 4 hypoglycemia seen in two patients, while temporally

Table 4. Serum cytokine measurements pre- and post-NK-92 doses. Cytokines were measured in the patients' sera before, 4 post- each of the three NK-92 infusions and at 7 days post-NK-92 infusion. Elevations in IL-6, IL-8 and IL-10 cytokines were seen with NK-92 infusion in the sample of four patients at the higher cell doses, with return to baseline by day 7

Patient	Diagnosis	Cell dose/ $m^2 \times 3$ doses	NK-92 infusion no.	IL-6* (pg/mL) Pre-	Post-	Day 7	IL-8* (pg/mL) Pre-	Post-	Day 7	IL-10* (pg/mL) Pre-	Post-	Day 7
8	RCC	1×10^9	1	34	71		5	15		< 3	< 3	
			2	215	94		11	6		< 3	4	
			3	125	214	35	9	12	10	< 3	< 3	< 3
9	RCC	1×10^9	1	282	307		339	298		41	22	
			2	291	276		257	327		7	74	
			3	284	286	282	299	309	305	7	24	9
10	Melanoma	3×10^9	1	17	18		20	24		< 3	< 3	
			2	46	29		27	19		66	44	
			3	17	6819	14	20	607	15	< 3	159	< 3
11	RCC	3×10^9	1	4	13		25	37		42	906	
			2	< 3	< 3		15	19		32	327	
			3	< 3	< 3	< 3	16	21	31	19	190	96

**The one-sided sign test has a P-value of 0.0625 for the average of pre–post differences.*

related to the NK-92 infusions, could be reflective of tumor lysis responses in these large tumor burden patients versus a reaction to the infusion of cells. The hypoglycemic response in patient 11, who had extensive liver metastases, could be related to tumor-induced hypoglycemia, which has been described in patients with extensive liver metastases [19]. Such a response could be the result of the release of insulin or a humoral hypoglycemic factor, such as an insulin-like substance or diminished glycogen stores in the liver from extensive metastases [19], or ectopic hormone production by the primary renal tumor, such as IGF-2, that can cause hypoglycemia [20]. Hypoglycemia in this setting might also be interpreted as a surrogate for a tumor lysis reaction [21], as may the increase in LDH seen in several patients after infusion of NK-92 . LDH increase is rather non-specific, however, and one cannot rule out other possibilities for the rise in LDH, such as from dead or dying NK-92 cells that were irradiated prior to infusion.

Similarly, elevations in IL-6, IL-8 and IL-10 with NK-92 infusion at the higher cell doses might suggest tumor lysis reaction. However, the cancers themselves can express these cytokines, as can the NK-92 cell line or a toxic response to the infusion of the cells, making it difficult to interpret the cytokine responses in a small sample of patients.

One patient developed HLA Ab whereas another did not. This result may point to a variability in the immune response to NK-92, and this may in part be explained by the variable host immunocompromised status. Other factors to consider are that prior blood product transfusions in the patient could induce an alloimmune response that is cross-reactive with those Ag expressed by NK-92. A larger number of patients will need to be studied to answer this issue. Still, there would seem to be a logical approach in avoiding retreatment of patients having a positive crossmatch beyond a 7-day window in order to prevent an anamnestic response.

The exact mechanism of NK-92 killing has not been established; however, it can be hypothesized that NK-92 essentially lacks KIR because of its immature status, and thus target killing is predominantly through its natural cytotoxicity receptors (NKp30 and NKp46) and activating receptor NKG2D [22], rather than a KIR-mediated NK alloreactivity mechanism. The clinical advantage may be that allogeneic NK cellular therapy with NK-92 has a broader spectrum of tumor killing because it overcomes the 'self' MHC molecule restriction, much as has been hypothesized for adoptive transfer of haplo-identical NK cells in patients with cancer [18,23].

Efficacy was not determined in this phase I trial; however, there were two patients with changes in tumor measurement that seemed to meet minor and mixed responses during the study period. These changes were, as expected, transient in this heavily pretreated population. Having determined the safety of infusion and feasibility of large-scale expansion in this initial study, the future plans with NK-92 include a phase II study to determine the biologic activity in other advanced cancers, and to draw on its unique advantage as a cell line to be a platform for genetic engineering to target tumor Ag, such as ErbB2 [24] and CD20 [25], to increase the potential for improved tumor localization and killing efficacy.

Acknowledgements

We thank the nurse practitioners, Kelly Kindy, Patricia Friend and Christina Havey, and staff of 10 Kellogg at Rush University Medical Center, Chicago, IL, for their help in co-ordination of patient care and data collection; Guitta Maki for NK-92 laboratory support; Michele Prod for technical HLA laboratory support, and Philip Lavori at Stanford for statistical consultation.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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EFS ID	4117342
Application Number	10008955
Confirmation Number	5420
Title	Natural killer cell lines and methods of use
First Named Inventor	Hans Klingemann
Customer Number or Correspondence Address	30058
Filed By	Christine W. Trebilcock/Dennis Ditzenberger
Attorney Docket Number	06-129 PCT/US/CIP
Filing Date	07-DEC-2001
Receipt Date	15-OCT-2008
Application Type	Utility under 35 USC 111(a)

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First Named Inventor/Applicant Name:	Hans Klingemann
Customer Number:	30058
Filer:	Christine W. Trebilcock/Dennis Ditzenberger
Filer Authorized By:	Christine W. Trebilcock
Attorney Docket Number:	06-129 PCT/US/CIP
Receipt Date:	15-OCT-2008
Filing Date:	07-DEC-2001
Time Stamp:	13:44:00
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Application Number:	10008955
Filing Date:	07-Dec-2001
Title of Invention:	COPY Natural killer cell lines and methods of use
First Named Inventor/Applicant Name:	Hans Klingemann
Filer:	Christine W. Trebilcock/Dennis Ditzenberger
Attorney Docket Number:	06-129 PCT/US/CIP

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Application Number	10008955	Filing Date	2001-12-07	Docket Number (if applicable)	06-129 PCT/US/CIP	Art Unit	1644
First Named Inventor	Hans Klingemann			Examiner Name	Ronald B. Schwadron		

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Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☒ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☒ Affidavit(s)/ Declaration(s)

☒ Other Submission of Amendment to Sequence Listing

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 032026

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Doc code: RCEX
Doc description: Request for Continued ... ...mination (RCE)

PTO/SB/30EFS (09-08)
...oved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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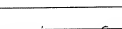
Signature of Registered U.S. Patent Practitioner			
Signature		Date (YYYY-MM-DD)	2008-10-15
Name	Christy Rothwell	Registration Number	55936

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	COPY
Hans Klingemann	
Serial No. 10/008,955	**NATURAL KILLER CELL LINES AND METHODS OF USE**
Filed: December 7, 2001	
Art Unit: 1644	
Patent Examiner: Ronald B. Schwadron	
Attorney Docket No. 06-129PCT/US/CIP	
Confirmation No.: 5420	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

October 15, 2008

SUBMISSION OF AMENDMENT TO SEQUENCE LISTING

This communication concerns the above-identified application.

Remarks begin on page 2 of this paper.

A paper copy of the Amended Sequence Listing is provided in **Appendix A** following page 4 of this paper.

A computer-readable format of the Amended Sequence Listing is filed herewith.

REMARKS

COPY

Amendment to the Sequence Listing

Applicant has amended the Sequence Listing to include "reverse primer" in SEQ ID NO: 2, section <223>, and has further amended the sequence listing to correct an inadvertent typographical error in <150> to read "PCT/US98/08672" to correctly identify the claim of priority to the International Application. Support for the amendments is found in the Substitute Specification filed on October 5, 2007, at least at pages 53 and 1, respectively. The amended Sequence Listing contains no new matter.

Applicant submits herewith a paper copy of the amended Sequence Listing in Appendix A following page 4 of this paper along with a computer-readable copy of the amended Sequence Listing. The copy in computer readable form is the same as the substitute copy of the Sequence Listing.

Conclusion

Applicant respectfully submits that the application and claims are in condition for allowance. Accordingly, reconsideration and allowance of all claims are respectfully requested.

Applicant would appreciate the courtesy of a telephone call should the Examiner have any questions or comments with respect to this submission for purposes of efficiently resolving same.

COPY

The Commissioner is hereby authorized to charge Deposit Account No. 03-2026 for any fees associated with this submission.

Respectfully submitted,

By _____

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(412) 297-4900

#1390820v1

APPENDIX A

SEQUENCE LISTING

<110> Klingemann, Hans

<120> Natural Killer Cell Lines and Methods of Use

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<151> 1999-10-27

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<151> 1998-04-30

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<212> DNA
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<220>
<223> reverse primer oligonucleotide based on human sequence

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